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Brief Communication: Comparative Mapping of the Human Estrogen Receptor (ESR) and the Kallmann (KAL) Regions to the Chromosomes of the Great Apes

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KEY WORDS estrogen receptor and Kallmann [KAL] regions; chimpanzee; gorilla; orangutan; chromosomes

ABSTRACT Human and great ape chromosomes display significant concordance by molecular and cytogenetic techniques, which may reflect their common origin. Nevertheless, chromosomal banding techniques did not reflect the syntenic homology at the DNA level, which created controversy and debate. The recent availability of the unique sequence loci-specific human estrogen receptor (ESR) (bq25.1) region and Kallmann (KAL) (Xp22.3) DNA probes have prompted us to search the degree of DNA sequence synteny among chimpanzee, gorilla, and orangutan by the FISH technique. The conservation of the ESR and Kallmann regions at the corresponding equivalent loci of the great ape chromosomes (5q25 and Xp22, respectively) has provided insights into genome evolution and facilitated assignment of map locations for human unique DNA sequences. These findings are aimed toward developing an augmented framework to determine with greater certainty the pathway of human descent at the single gene level. Am J Phys Anthropol 103:561–563, 1997.

Classical cytogenetic techniques have demonstrated extensive homology between human and chimpanzee chromosomes. Nevertheless, a better understanding of exact DNA correspondences and the mechanisms of chromosome evolution is needed if we aim to establish hominoid phylogenetic relationships. This study provides a step in this direction by seeking similarities and differences among hominoids at a finer resolution than classical cytogenetic methods allow. Specifically, the study deciphers sequence synteny within two loci—the human estrogen receptor (ESR) and the Kallmann (KAL) locus—among humans and the great apes.

ESR AND KAL GENES

The human estrogen receptor (ESR) is a member of a family of nuclear receptors for small hydrophobic ligands including the steroid hormones, thyroid hormone, vitamin D, and retinoic acid. The receptor was first identified in the 1960s, and a relationship between estrogen receptor expression in the primary breast tumor and subsequent response to endocrine therapy was demonstrated. The ESR gene has been mapped to human chromosome 6q25.1 (Menasce et al., 1993). The ESR gene is more than 140 kb long and split into eight exons, and the positions of the introns have been highly conserved, being remarkably similar to those of the chicken thyroid hormone receptor genes (Ponglikitmongkol et al., 1988). Also, estrogen receptor mRNA expression has been reported in murine mammals (Bhat et al., 1993).

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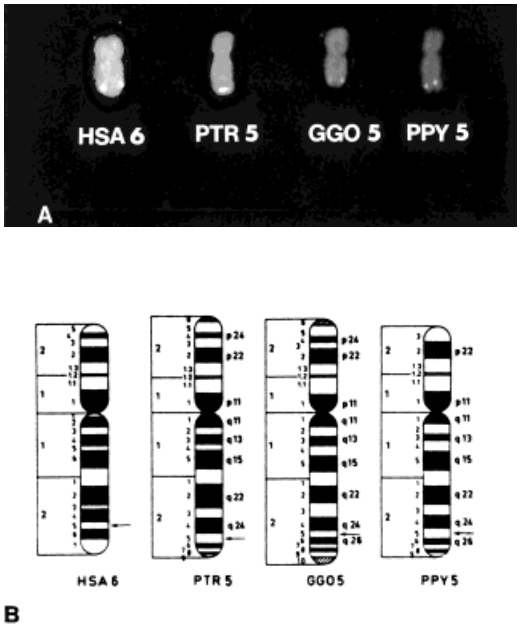

Fig. 1. **A:** Location of estrogen receptor gene on chromosomes of human (HSA 6), chimpanzee (PTR 5), gorilla (GGO 5), and orangutan (PPY 5) individuals. **B:** Diagrammatic representation of chromosome bands of human chromosome 6 and apes' equivalent chromosome 5 (ISCN, 1985). The location of the estrogen receptor gene is arbitrarily assigned.

Kallmann syndrome refers to a disorder characterized by hypogonadotropic hypogonadism and anosmia. The disorder is due to Xp22.3 deletions and follows several modes of inheritance, with the X-linked mode the most frequent (for review see McKusick, 1994). The Kallmann (KAL) gene has been mapped to the Xp22.3 region (Meitinger et al., 1990; Rugarli and Ballabio, 1993). Its locus is 350 kb in length, located between 8,600 and 8,950 kb from Xpter. The KAL gene consists of 14 exons spanning 120–200 kb that correlate with the distribution of domains in the predicted protein including four fibronectin type III repeats (Del Castillo et al., 1992). There is a 73 and 72% overall identity of chicken and quail KAL cDNAs, respectively, with human KAL cDNA (Legouis et al., 1993).

By molecular and cytogenetic techniques, human chromosomes 6 and X share similar chromosomal banding patterns and DNA sequence homology with chromosome 5 and X, respectively, of chimpanzees (*Pan troglodytes*), gorillas (*Gorilla gorilla*), and orangutans (*Pongo pygmaeus*) (ISCN, 1985; Goodman et al., 1989; Wienberg et al., 1990; Wienberg and Stanyon, 1995). The recent availability of nonradioactive DNA probes for the human ESR and KAL regions prompted us to hybridize it to the aforementioned primate chromosomes 5 and X to search for its corresponding location.

MATERIALS AND METHODS

Ape chromosomes were obtained from fibroblast cell lines (Coriell Cell Repositories, Camden, NJ) of chimpanzees (AGO 3450, *Pan troglodytes*) (PTR), gorillas (AGO 5351, *Gorilla gorilla*, GGO), and orangutans (AGO 4742, *Pongo pygmaeus* (PPY) using standard procedures. Human chromosomes (*Homo sapiens*) (HSA) were prepared from phytohemagglutinin-stimulated blood lymphocytes from normal individuals (Verma and Babu, 1995). The FISH technique (Lichter et al., 1995) was employed with minor modifications. For localizing the Kallmann region, the digoxigenin-labeled Kall-

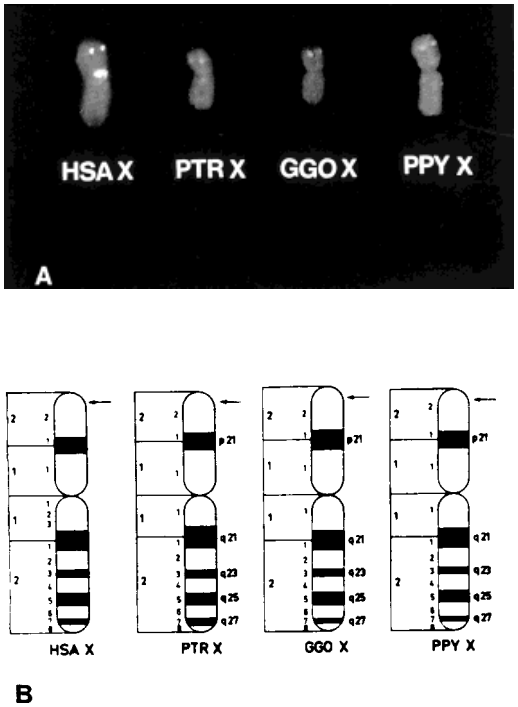

Fig. 2. **A:** Location of the Kallmann region on chromosomes of human (HSA X), chimpanzee (PTR X), gorilla (GGO X), and orangutan (PPY X) individuals. **B:** Diagrammatic representation of chromosome bands of human chromosome X and apes' equivalent chromosome X (ISCN, 1985). The location of the Kallmann region is arbitrarily assigned.

mann (KAL) Xp22.3 region DNA probe with a DXZ1 chromosome X control probe (Oncor, Gaithersburg, MD) was used. For localizing the estrogen receptor (ESR) region, the digoxigenin-labeled estrogen receptor DNA probe specific for locus 6q25.1 (Oncor) was used.

RESULTS AND DISCUSSION

Hybridization data obtained by comparative mapping using the FISH technique illustrates that the human genome is closely related to that of the great apes by the presence of similar DNA sequences for the estrogen receptor and Kallmann regions. The ESR region has been localized to band 6q25.1 in the humans (HSA 6) and to band 5q25 of the equivalent chromosomes in chimpanzees (PTR 5), gorillas (GGO 5), and orangutans (PPY 5) (Fig. 1). The Kallmann region has been localized to band Xp22.3 in humans (HSA X) and to band Xp22 in the equivalent chromosomes of chimpanzees (PTR X), gorillas (GGO X), and orangutans (PPY X) (Fig. 2). No hybridization signals were observed for the DXZ1 chromosome X control probe in the ape chromosomes. The present approach provides another phylogenetic parameter for interspecific comparison. Loci-specific human DNA probes have been used to further narrow the gaps of genotypic divergence among humans and apes as the chromosomal basis of identity has always been challenged (King and Wilson, 1975; Yunis and Prakash, 1982; Luke and Verma, 1993; Luke and Verma, 1995; Verma and Luke, 1994). Such techniques facilitate investigations on the degree of DNA sequence synteny between humans and the great apes and permit insights into their genome evolution. In addition, it is possible that these higher non-human primates may serve as models in studies involving these genetic disorders. Evidently, such DNA sequences have been conserved during the process of human descent. The study of evolutionary relationships of closely related primates with the use of specific single gene unique sequence probes may reveal pathways of concerted evolution.

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